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REMARKS

Claims 1 and 3-17 are pending. No amendments have been made by way of this response. Thus, no new matter has been added. Claims 1 and 3-17 remain present for examination.

Claims 1 and 3-17 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hellstrand *et al.* (U.S. Patent No. 6,071,942). Applicants disagree with this rejection and respectfully request reconsideration and withdrawal of the present rejection in view of the comments below.

Claims 1 and 3-17 are non-obvious in view of Hellstrand *et al.* (U.S. Patent No. 6,071,942)

The Patent Office has maintained the rejection of Claims 1 and 3-17 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hellstrand *et al.* (U.S. Patent No. 6,071,942) (the '942 patent). Specifically, the Patent Office alleges that the '942 patent is drawn to a composition comprising histamine, histamine dihydrochloride, histamine phosphate and other salts, esters and congeners (col. 19, line 21) in a transmucosal formulation (col. 19, lines 5-10), further comprising pharmaceutically active agents such as chemotherapy agents (examples), and further comprising penetration enhancers such as dimethylsulfoxide (col. 18, lines 31-35). The Patent Office notes that the reference does not disclose the percentages recited in the claims, but alleges that such limitations are merely optimization of parameters that can be determined through routine experimentation by one of ordinary skill in the art. Applicants disagree and maintain that the pending claims are non-obvious in view of the '942 patent.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

In response to Applicants' arguments regarding the lack of motivation to modify the reference and the lack of a reasonable expectation of success in doing so, the Patent Office maintains that the motivation to modify the '942 patent would be to optimize the release of the active ingredient and to maximize the effectiveness of the formulation described therein. The

Patent Office further argues that varying the concentrations of the formulation would fall in the realm of routine experimentation, which is not patentable absent a showing of unexpected results. Applicants submit that the Patent Office is using improper standards and flawed reasoning in maintaining this rejection.

Applicants again remind the Patent Office that it is well-established that before optimum ranges or values of a particular variable are characterized as a result of routine experimentation, the variable must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result. *See* M.P.E.P § 2144.05(II)(B) citing *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977). In *In re Antonie*, the applicant had discovered an optimum ratio of tank volume to contractor area (0.12 gal./sq ft) which maximized treatment capacity of a wastewater treatment device. While the prior art disclosed tank volume and contractor area, the C.C.P.A. allowed the claims because the prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio. In other words, the optimized ratio was not recognized in the art to be a result-effective variable.

The claims of the instant application are directed to a transmucosally administrable composition comprising a pharmaceutically active compound and a permeation enhancer such as histamine, histamine phosphate, or histamine dihydrochloride, wherein the permeation enhancing agent acts to facilitate the delivery of a pharmaceutical compound transmucosally. The claimed invention is based on the unexpected and previously unknown property of histamine to enhance the delivery of pharmaceutically active compounds through mucosal membranes and into the bloodstream. Histamine, an inflammatory mediator, enhances tissue uptake of a pharmaceutically effective agent such as a chemotherapeutic. Its effect on fine vessels is to cause edema by increasing the flow of lymph and lymph proteins into the extracellular space and also by promoting the formation of gaps between endothelial cells, thus increasing transcapillary vesicular transport. The present invention is based in part on the discovery that histamine can enhance the permeation of a pharmaceutically active compound across a transmucosal membrane and across mucosal membranes. The same mechanism by which histamine and histamine-like compounds cause edema in fine vessels can be harnessed to increase drug concentrations in, for example, tumor tissues. The beneficial role of histamine in the claimed invention therefore

relates to its unexpected ability to facilitate the transport of a pharmaceutically active agent such as a chemotherapeutic into the bloodstream.

Applicants maintain that the prior art did not recognize and/or appreciate that histamine could be used as a permeation enhancing agent and therefore did not recognize the permeation enhancement properties of histamine as result-effective variables to be optimized. Applicants were the first to discover that a composition comprising histamine or a histamine-related compound, having about 0.001% to about 25 % weight/volume of the total composition, has the novel and unexpected property of enhancing the transmucosal delivery of a drug or vaccine. This range of concentrations and the effect on permeation enhancement are both novel and non-obvious in view of the '942 patent.

In fact, the '942 patent is silent with respect to the advantages of a transmucosally administrable composition comprising a permeation enhancing agent such as histamine in combination with another pharmaceutically active compound. Instead, the thrust of the '942 patent is directed at achieving stable, elevated blood histamine levels in order to stimulate NK cell activity and cytotoxic T-lymphocyte (CTL) cytotoxicity through the suppression of an inhibitory signal generated by monocytes. *See* Col. 3, lines 55-67 of the '942 patent. The inhibitory effects of monocytes on cytotoxic effector cells such as NK cells and CTLs were believed to result from the generation of hydrogen peroxide by monocytes. By injecting histamine such that a stable, elevated level of blood histamine was achieved, histamine would reduce the level of hydrogen peroxide produced by monocytes, thereby removing the inhibitory effects of monocytes and augmenting the activity of NK cells and CTLs. Thus, in the context of the '942 patent, histamine acted as the pharmaceutically effective agent for treating, *inter alia*, malignancies or viral infections through the promotion of NK cell and CTL activation rather than as a permeation enhancing agent. Notably, the '942 patent is silent with respect to any permeation enhancing properties of histamine.

In contrast, the claims of the present invention are directed to transmuscosally administrable compositions comprising a pharmaceutically active compound and a permeation enhancing agent such as histamine. Transmucosal administration of a pharmaceutically active compound facilitated by histamine is quite different from administration of histamine as the active ingredient via injection. The desirability of utilizing histamine or histamine-like

compounds as permeation enhancing agents for transmucosal administration of a different active compound was neither recognized nor suggested by the '942 patent.

Because the '942 patent contains no suggestion that histamine could be used as a permeation enhancing agent it therefore does not recognize the permeation enhancement properties of histamine as a result-effective variable to be optimized. In fact, the use of a permeation enhancing agent wherein the agent is selected from the group consisting of histamine and histamine agonists is a feature taught only by the instant application. With no disclosure or suggestion that histamine could serve as a permeation enhancing agent in the '942 patent, a skilled artisan would not be motivated by the reference to optimize the transmucosal dose of histamine needed to produce the optimal level of permeation enhancement by histamine.

In spite of these deficiencies in the '942 patent, the Patent Office maintains that one of ordinary skill in the art could optimize the formulation described therein to produce the optimal level of permeation enhancement by histamine. Applicants strongly disagree and submit that the motivation to use histamine as a permeation enhancing agent and to optimize the level of such enhancement comes from Applicants' specification

Applicants remind the Patent Office that it is improper to glean knowledge from Applicants' disclosure and use it with a cited reference to construct an obviousness rejection. M.P.E.P. § 2145 (citing *In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (C.C.P.A. 1971)). The content of the prior art must be determined at the time the invention was made, so as to avoid impermissible hindsight. Moreover, where the prior art gives not indication of which parameters are critical, it would not be obvious or routine to vary all of the parameters to arrive at a successful result. M.P.E.P. § 2145.

The Patent Office has improperly read the use of histamine and histamine agonists as permeation enhancing agents into the prior art. In addition, the Patent Office has characterized the optimization of the level of permeation enhancement by histamine as routine. In so doing, the Patent Office has engaged in impermissible hindsight reasoning. Accordingly, it is improper to base an obviousness rejection on the '942 patent.

The Patent Office indicates that absent a showing of an unexpected result, such as a high, more sustained blood concentration resulting from the combination, it will remain the position of the Examiner that the general teachings of the '942 patent obviate the instant claims.

While Applicants maintain that this rejection is improper for the reasons discussed above, in the interest of advancing the application to allowance, Applicants submit herewith as evidence of the nonobviousness of the claims, articles detailing the unexpected ability of histamine to facilitate the transport of a pharmaceutically active agent, such as a chemotherapeutic agent. Accordingly, enclosed herewith is a recent publication which details the synergistic anti-tumor activity of histamine plus a chemotherapeutic agent in isolated limb perfusion. Brunstein *et al.*, *J Natl Cancer Inst* 2004;96(21):1603-10 ("EXHIBIT A"). As indicated on page 1608 of the article, the authors observed an increase in chemotherapeutic concentration in tumors. Specifically, histopathological examination revealed that histamine administration resulted in a dramatic increase in permeability of methalpan on the order of four- to five-fold. Thus, the authors demonstrate the unexpected advantages of histamine and histamine-like compounds on permeation enhancement. Also enclosed herewith is an unpublished article by the same authors, which demonstrates that this effect of histamine on permeation enhancement was not restricted to methalpan, but was also present in combination with doxorubicin, another chemotherapeutic agent. Brunstein *et al.*, unpublished ("EXHIBIT B").

These references demonstrate a dramatic increase in the permeability of two different pharmaceutically active compounds when administered in combination with histamine as compared to administration of any of the agents alone. Thus, Applicants have demonstrated a greater than additive effect of histamine as a permeation enhancer. Moreover, as discussed above, this effect of histamine was unrecognized in the prior art, and thus, this striking effect was unexpected. Finally, the enclosed articles set forth in their respective Discussion sections that the unexpected effects of histamine as a permeation enhancing agent are of significant, practical advantage. Applicants have provided a strong showing of unexpected results that are of significant, practical advantage, thereby demonstrating that the claimed invention is not obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

Applicants maintain that the '942 patent is silent with respect to the permeation enhancing properties of histamine. Without any evidence that histamine can enhance the permeation of or the entry into the dermal or mucosal layers by other pharmaceutically active agents, the '942 patent fails to teach or suggest the limitations of the present claims. Moreover, Applicants maintain that the disclosure in the '942 patent cannot provide a basis for finding the

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optimal dosage of histamine as a permeation enhancer. Additionally, Applicants submit herewith evidence of dramatic unexpected results of the claimed compositions and the significant advantage of such compositions, thereby providing a further patentable distinction between the formulation of the instant claims and that of the '942 patent. For these reasons, Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103 and allowance of the application.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejection set forth in the outstanding Office Action has been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

Applicants have endeavored to address all issues raised in the Office Action. Nevertheless, if the Patent Office finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Patent Office is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Nov. 23, 2005

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